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José Miguel Barreto Bernardo

Manifestações neonatais de doenças imunomediadas reumatológicas: um estudo retrospetivo longitudinal num hospital terciário/ Neonatal manifestations of immune-mediated rheumatic diseases: a retrospective longitudinal study in a tertiary hospital

março, 2017

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DESIGNAÇÃO DA ÁREA DO PROJECTO

Reumatologia

TÍTULO DISSERTAÇÃO

Neonatal manifestations of immune-mediated rheumatic diseases: a retrospective longitudinal study in a tertiary hospital

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À mulher mais bonita do mundo,
que me protegeu durante nove meses
e que o continua a fazer
há mais de vinte e quatro anos.

e

Ao homem mais corajoso que conheço,
que é capaz de abdicar de tudo pela família,
e me ensinou o valor mais importante do mundo:
a humildade.

Title: Neonatal manifestations of immune-mediated rheumatic diseases: a retrospective longitudinal study in a tertiary hospital

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ABSTRACT

INTRODUCTION: Autoimmune rheumatic diseases such as systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS) and Sjögren's syndrome (SS) are part of a clinical spectrum which affects women in child-bearing age, affecting pregnancy and neonatal outcome. Preterm birth, foetal growth restriction (FGR) and neonatal lupus (NL) – cardiac, cutaneous, haematological, hepatic and, more rarely, pulmonary manifestations – have been described.

OBJECTIVE: This study aims to evaluate pregnancy outcome focusing on preterm birth and FGR of rheumatologic immune-mediated diseases in the mother and on neonatal manifestations in their babies in "Centro Hospitalar São João", Porto, Portugal, between 2010 and 2015.

METHODS: A retrospective longitudinal study was performed including pregnant women with immune-mediated rheumatic diseases seen by a multidisciplinary team for pregnancy surveillance of women with autoimmune diseases. Data was collected through consultation of clinical files. Pregnancy outcome such as preterm birth and FGR and babies with and without NL were compared between themselves using Mann-Whitney, chi-square and Fisher tests. Significance level was set at $p<0.05$.

RESULTS: 140 women had 147 gestations, including 4 twin pregnancies, and delivered 142 live born babies; 7 (4.6%) abortions and 2 (1.3%) stillbirths occurred. During gestation, 54 (35.8%) foetuses' mothers had SLE, 41 had (27.2%) APS, 17 (11.3%) had SS, 17 (11.3%) had RA, 11 (7.3%) had Behçet's disease, 8 had (5.3%) mixed connective tissue disorders, 4 had (2.6%) systemic sclerosis, and 16 (10.6%) had other immune-mediated diseases. Thirty-five (23.2%) had anti-SSA/La antibodies and 18 (11.9%) had anti-SSB antibodies. Nineteen (13.2%) foetuses had FGR during gestation and 28 (19.7%) were delivered before term. Six (4.2%) neonates were born with NL and 1 (0.7%) died *in utero* with a complete heart block (CHB). Out of these 7 babies with NL, 5 (71.4%) had cardiac, 2 had (28.6%) cutaneous, 1 (14.3%) had hepatic, 2 (28.6%) had haematological and 1 (14.3%) had pulmonary manifestations. Preterm birth and FGR occurred less frequently among women who had a preconception appointment (0.0% vs. 27.2%; $p=0.004$ and 7.1% vs. 28.1%; $p=0.013$, respectively). FGR occurred less among women with rheumatic diseases in remission at conception (7.1% vs. 23.7% $p=0.038$). NL manifestations occurred more frequently in mothers with SS (57.1% vs. 8.8%; $p=0.003$) and FGR (42.9% vs. 11.7%; $p=0.049$).

CONCLUSION: Our study proved a link between immune-mediated rheumatic diseases and specific pregnancy outcome like preterm birth, FGR and NL. These may be altered if women attend a preconception appointment and plan pregnancy, conceiving at a remission period of the disease. FGR associated with anti-SSa/Ro and anti-SSb/La antibodies may be considered a predicting factor for NL. Multidisciplinary pre-pregnancy counselling as well as rheumatologic and obstetric surveillance should be recommended to all women with immune-mediated rheumatic diseases.

KEYWORDS: preterm birth, fetal growth restriction, neonatal lupus, pregnancy outcome, neonatal outcome, preconception

1. Introduction

Autoimmune rheumatic diseases such as systemic lupus erythematosus (SLE), anti-phospholipid syndrome (APS), rheumatoid arthritis (RA) and Sjögren's syndrome (SS) are part of a clinical spectrum which affects women in child-bearing age. SLE, APS and RA have been more intensively studied regarding pregnancy and neonatal impact as they are the most frequent immune-mediated diseases to occur during this period.

When pregnancy co-exists with this set of pathologies, severe maternal-foetal complications may arise, not only derived from the disease itself, but also as a consequence of administered drugs, such as anti-inflammatory, immunosuppressive and disease-modifying drugs [1] and incorrect conception planning. SLE has been shown to increase the risk of recurrent pregnancy loss, foetal loss, preterm birth, preeclampsia and foetal growth restriction (FGR) [2-5]. APS, for instance, is associated with an increased prevalence of recurrent spontaneous pregnancy loss and FGR, possibly due to thrombosis of placental vessels [6, 7]. RA usually presents good pregnancy outcome with less symptomatology and need of analgesic drugs [8]. Smaller birthweight has also been reported in primary SS [9]. Nonetheless, if conceiving occurs during a period of remission, these complications occur less frequently [2, 4]. The remaining diseases lack evidence regarding maternal-foetal consequences.

Autoimmune diseases that are seropositive for specific antibodies during pregnancy may also lead to transplacental transfer of maternal IgG antibodies to the foetal circulation, originating neonatal autoimmune diseases [10]. The most common is neonatal lupus (NL) that usually expresses itself as complete heart block (CHB) and/or cutaneous rash, but may also express as hepatobiliary disease and/or cytopenia [11]. It can occur among mothers with anti-SSa/Ro and anti-SSb/La antibodies, which are more frequent in SLE, APS and SS, but may also be present in other connective tissue disorders [12]. Environmental and foetal genetic factors, namely B-cell, complement or interferon (IFN) activation and inflammation may also contribute to the pathogenesis of the disease [9, 13].

Cutaneous NL usually presents at 6 weeks of life or later [14] and tends to dissipate at around 17 weeks, when maternal antibodies disappear from the foetal circulation [15]. Skin lesions consist of erythematous annular and scalous plaques with a central clearing. They are frequently found on the face and scalp and less frequently on the arms, legs and trunk [13, 16]. Photosensitivity is also a frequent finding, as it is considered a trigger for cutaneous lesions, although it is difficult to evaluate [15]. Even though these are transient, atrophic and scarring lesions, telangiectasia, hypopigmentation and alopecia may persist [17].

Anti-SSA/Ro and anti-SSB/La antibodies accumulate around the AV node conduction system [18], promoting inflammation, scarring and fibrosis [19]. This manifestation, the second most common after cutaneous NL, can presents itself as first-, second-, or third-degree (complete) heart block and may be diagnosed *in utero* or postnatally [14]. Around 70% of affected children require pacemaker [20]. Neonates may also develop diffuse cardiomyopathies [21], endocardial fibroelastosis [22], prolonged QT interval [23] and sinus bradycardia [24].

Regarding liver involvement, NL may either present as neonatal haemochromatosis, in which liver failure occurs *in utero* or after birth, or as cholestasis with conjugated hyperbilirubinemia and minimal or transient transaminase elevations a few weeks after birth [13, 16]. Other studies also report liver enlargement [25, 26].

Concerning haematological complications, research has shown that some blood cells contain a Ro cross-reactive protein [27]. Although they may not be present at birth, they may develop over time. Clinical manifestations include self-limiting mild anaemia and thrombocytopenia, which resolve in 2 to 3 months [28].

This study aims to evaluate pregnancy outcome focusing on preterm birth and FGR of rheumatologic immune-mediated diseases in the mother and on neonatal manifestations in their babies in “Centro Hospitalar São João”, Porto, Portugal, between 2010 and 2015. Maternal outcome as hypertensive disorders of pregnancy and the occurrence of lupus flares were not considered for the purpose of this study.

2. Materials and Methods

A retrospective longitudinal study was performed.

2.1 Patients

We included pregnant women with the following immune-mediated rheumatic diseases: SLE, SS, RA, APS, Behçet's disease, systemic sclerosis, polymyositis/ dermatomyositis, mixed connective tissue disorders, reactive, psoriatic and juvenile arthritis, vasculitis and spondylitis that were seen by a multidisciplinary team for autoimmune diseases during pregnancy between January 2010 and December 2015. This multidisciplinary team consists of a consultant obstetrician and a senior internist. Women who are pregnant are referred to this group by dermatology, internal medicine, rheumatology and nephrology.

All gestations of women seen at a first appointment, who had a definite diagnosis at the time of pregnancy and had their baby in "Centro Hospitalar São João" were included. Time-separated gestations of the same woman during our period of study were also considered separate. We therefore included 140 women who had a total of 147 gestations and delivered 151 babies; 4 twin pregnancies were included.

We excluded women who only had preconception appointment but did not subsequently become pregnant, women who did not have a definite autoimmune rheumatic diagnosis and gestations that were lost in follow-up.

2.2 Clinical data

Clinical and demographic data as well as pregnancy and neonatal outcome were collected through consultation of clinical files and the obstetrics surveillance software ObsCare®. We consulted relevant demographic data from mothers and their babies, occurrences of the present gestation – therapeutic drugs, social habits, autoantibody profile, gestational age at birth and weight at delivery. Preterm birth was considered birth before the 37th week of gestation ($\leq 36^{+6}$ weeks) and FGR as the estimated foetal weight $<P_5$ for gestational age at ultrasound as defined in the department of Gynaecology/ Obstetrics of this hospital. Other relevant details, background and neonatal manifestations were also consulted. This research project was approved by the local ethics committee.

2.2.1. Statistical analysis

Statistical analysis was performed using IBM SPSS statistics 24.0. Patients with and without NL were compared using Mann-Whitney, chi-square and Fisher tests. Factors associated with pregnancy outcome were studied using the same tests. Significance level was set as $p<0.05$.

3. Results

3.1. Descriptive and demographic analysis

During the period of study, 140 women with a mean age of 32,5 ± 4,4 years had 147 gestations and delivered 142 babies; 7 (4.6%) gestations ended as abortions and 2 (1.3%) resulted in stillbirths. Four women had twin pregnancies. Fifty-four (35.8%) women had SLE, 41 had APS (27.2%), 17 (11.3%) had SS, 17 (11.3%) had RA, 11 (7.3%) had Behçet's disease, 8 (5.3%) had mixed connective tissue diseases, 4 (2.6%) had systemic sclerosis, 0 (0.0%) had polymyositis/ dermatomyositis, and 16 (10,6%) had other immune-mediated diseases described in section 2.1. Thirty-five (23.2%) babies were exposed to anti-SSA/La antibodies during pregnancy and 18 (11.9%) to anti-SSB/Ro antibodies. Thirty-six (23.8%) of the gestations were seen at a preconception appointment and 29 (19.2%) were in a period of remission at the time of conception. For further demographic and gestation details, please refer to table 1.

The mean gestational age of birth was $37^{+4} \pm 1^{+6}$ weeks. Eighty (53.0%) babies were born male. The mean length was 47.5 ± 3.5 cm (lowest: 28.0cm; highest: 52.5 cm), the mean weight was 2813.0 ± 533.4 g (lowest: 555.0g; highest: 4140.0g) and the mean head circumference was 33.5 ± 1.9 cm (lowest: 21.5cm; highest: 38.0cm). Twenty-eight (19.7%) babies were born preterm and 25 (17.6%) were admitted in the neonatal intensive care unit (NICU). A total of 7 (4.6%) babies had NL; 1 (0.7%) of them died *in utero* on week 33^{+4}. Concerning immunological profile, apart from anti-SSa and anti-SSb antibodies, 2 (1.4%) babies were ANA positive, 1 (0.7%) was anti-dsDNA positive and 1 (0.7%) was IgM/IgG positive. For further details regarding demographics and neonatal manifestations, please refer to table 2.

3.2. Pregnancy outcome

FGR and preterm birth occurred less frequently among mothers who were seen at a preconception appointment (0.0% vs. 27.2%; p=0.004 and 7.1% vs. 28.1%; p=0.013, respectively). Babies with FGR were more frequently admitted in the NICU (52.6% vs. 12.0%; p<0.001). Preterm birth occurred less frequently among mothers who were in remission period of the disease at the time of conception (7.1% vs. 23.7%; p=0.038). Please refer to table 3 for further details regarding FGR and preterm birth.

3.3. Neonatal outcome

Babies with NL were more frequently growth restricted (42.9% vs. 11.7%; p=0.049) and were admitted in the NICU more often (71.4% vs. 14.6%; p=0.002). Concerning immunological profile in babies with NL, apart from anti-SSa/Ro and anti-SSb/La, some antibodies were seen more frequently: anti-DNAds (14.3% vs. 0.0%; p=0.046), anti-ß2GP (14.3% vs. 0.0%; p=0.046) and ANA's (28.6% vs. 0.0%; p=0.002). Other relevant details regarding NL may be found in table 4.

4. Discussion

Women with immune-mediated rheumatic diseases are indeed more vulnerable to poor pregnancy and neonatal outcome. As Chen et al concluded, infants are at increased risk of preterm birth and admission in the NICU [29]. For instance, hypertensive complications in SLE have been shown to increase the risk of preterm birth, FGR and foetal loss [30, 31]. Our study was not aimed at evaluating hypertensive complications; however, it does prove the association between FGR and preterm birth and factors associated with autoimmune diseases.

Given that a considerable number of women must maintain their normal glucocorticoid intake during pregnancy for autoimmune disease control (53.6%), they become exposed to a greater risk of preterm birth and FGR. Furthermore, even though no association was found between autoimmune rheumatic diseases and gestational diabetes, the latter increases the probability of FGR.

Statistical significance was found between FGR and babies who were born before term. Even though literature provides a link between autoimmune rheumatic diseases and FGR [6, 32, 33], this study failed to show this association.

Women who had preterm births visited the doctor less frequently for pre-pregnancy counselling, possibly leading to conceiving in periods of active disease due to lack of compliance, whereas they should conceive in periods of remission, as reinforced by this study.

Similar to the statistically significant results for preterm birth, none of the women whose babies developed FGR were seen at a preconception appointment, even though no association was found between this neonatal outcome and women who conceived in a remission period of the disease. Regarding autoantibody profile, no statistically significant association was found between the antibodies listed in *table 1* and the aforementioned pregnancy outcome.

Considering that only mothers with positive anti-SSA/Ro and anti-SSb/La antibodies may have babies with NL, it is noteworthy that out of 35 (23.1%) gestations positive for these antibodies, 7 (20.0%) babies developed the disease. Literature is consensual when describing the incidence of neonatal lupus in the offspring of mothers with anti-SSA/SSB antibodies, which stands between 1-3% [20, 34, 35] but may reach >20% if the mother has previously delivered a child with CHB before [36]. According to our study, recurrence occurred in 33% of the cases, although the sample is not significant and further conclusions cannot be made.

Moreover, in accordance to what has been previously reported, transplacental passage of antibodies to the foetus does not always occur, indicating that environmental factors may interfere; nonetheless, these remain unknown and future research should address this matter. In our tertiary care facility, it is protocol to screen for anti-SSa/Ro and anti-SSb/La antibodies in babies whose mothers test positive during pregnancy. None of the babies, whose mothers were positive for anti-SSa and anti-SSb antibodies during pregnancy, but who did not develop NL, were positive for these antibodies, indicating that their passage occurs during gestation and excluding the possibility that babies may be asymptomatic carriers. It is also worthy of mention that one of the cases of NL

occurred in a baby that was born from a twin gestation. Despite both being exposed to the same environment, only one of the twins received the antibodies and developed NL. This case might be interesting for future studies.

Although many autoimmune diseases may present with anti-SSa/Ro and anti-SSb/La antibodies, we only found an association with SS. Neither SLE or APS presented a significant association.

The fact that babies with NL were born smaller, with lower Apgar scores at minute 10 and with a higher admission rate in the NICU might be explained by the fact that 5 of the 7 cases of NL had CHB, which indicates poorer birth outcome. Despite the lack of association with immunological profile or pregnancy events, one of the babies was born with cardiac, haematological, hepatic and pulmonary manifestations. Along with aseptic meningitis, myelopathy, lymphadenopathy and chondrodysplasia punctata, lupic pneumonitis is a very rare manifestation. Their underlying mechanism has so far not been found [37, 38].

What the authors did find interesting was the association of other autoantibodies like anti-dsDNA, anti-ß2GP and ANA's with NL. No data is found in literature regarding this association and unfortunately our sample is too small to allow for a definite conclusion. Further research should focus on the co-immunological manifestation of anti-SSa/Ro and anti-SSb/La antibodies with either ANA's, anti-ß2GP and anti-dsDNA antibodies to determine their influence on NL expression.

4.1. Sources of error

The main drawback of this study lies on its retrospective nature. Furthermore, due to the specialized counselling in pregnancy-related autoimmune diseases that our multidisciplinary team offers, subjects from this study do not represent the general population and therefore constitute a selection bias with overestimation of results.

4.2. Sources of improvement

The multidisciplinary team for autoimmune diseases in pregnancy was established in April 2009 which impeded this study from analysing a larger sample. This study should be run in roughly 10 years' time to do so. Furthermore, this study should be carried out as a multicentre analysis to eliminate result overestimation. Studies should also compare tertiary hospitals with and without a multidisciplinary team for immune-mediated diseases in pregnancy to determine differences in approach leading to different possible outcome.

5. Conclusions

Our study proved that:

1. Multidisciplinary pre-pregnancy counselling as well as rheumatologic and obstetric surveillance should be recommended to all women with immune-mediated rheumatic diseases. During the preconception appointment, women should be advised not to conceive while in an active period of disease. Conceiving during this period undoubtedly increases glucocorticoid intake during pregnancy and consequently the risk of preterm birth, FGR and admission in the NICU, thus increasing hospital stay, costs and exposure to multi-resistant pathogens. Careful surveillance during pregnancy also leads to a better control of gestational diabetes, hence decreasing the risk of FGR.

2. Mothers with previous children with the disease should be carefully advised when planning a future pregnancy given the high risk of recurrence.

3. According to the results, FGR associated with anti-SSa/Ro and anti-SSb/La may be considered a predicting factor for NL. Babies whose mothers carry the antibodies and have FGR during pregnancy should therefore be more prominently studied.

4. Besides anti-SSa and anti-SSB, there is an association between NL and ANA's, anti-ß2GP and anti-dsDNA antibodies. Further research should focus on the influence of immunological profile in the expression of NL.

Highlights

1. FGR associated with anti-SSa and -SSb antibodies may be predictive factor of NL.
2. There is an association between NL and ANA's, anti-ß2GP and anti-dsDNA antibodies.
3. Multidisciplinary pre-pregnancy counselling should be recommended.

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Competing interests

None.

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Table 1: Demographic, clinical and immunological characteristics of mothers.

Mother characteristics	
Age at first appointment, *mean ± SD (years)*	32.5 ± 4.4
BMI at first appointment, *mean ± SD (kg/m^2)*	26.2 ± 5.4
Presence of previous miscarriages, *n (%)*	54 (35.8%)
Years of disease evolution, *mean ± SD*	6.0 ± 2.9
Immune-mediated rheumatic diseases, *n (%)*	
Systemic lupus erythematosus	54 (35.8%)
Anti-phospholipid syndrome	41 (27.2%)
Sjörgen's syndrome	17 (11.3%)
Rheumatoid arthritis	17 (11.3%)
Behçet's disease	11 (7.3%)
Systemic sclerosis	4 (2.6%)
Polyomiositis/ dermatomyositis	0 (0.0%)
Mixed connective tissue diseases	8 (5.3%)
Other autoimmune diseases	16 (10.6%)
Immunological manifestations during pregnancy, *n (%)*	
Anti-dsDNA positive	22 (14.6%)
Anti-SSA/Ro positive	35 (23.2%)
Anti-SSB/La positive	18 (11.9%)
Anti-U1RNP positive	6 (4.0%)
Lupus anticoagulant positive	16 (10.6%)
IgG/IgM anticardiolipin positive	35 (23.2%)
IgM/IgG anti-ß2GP positive	28 (18.6%)
Drug administration during pregnancy, *n (%)*	
Glucocorticoids	81 (53.6%)
NSAID's	9 (6.0%)
Immunosuppressive drugs	9 (6.0%)
Pregnancy outcome, *n (%)*	
Gestational diabetes	7 (4.6%)
Gestational hypertension	5 (3.3%)
FGR	19 (13.2%)
Lupic flare	10 (6.6%)
Miscarriage	9 (6.0%)
Other relevant details, *n (%)*	
Pre-conception appointment	36 (23.8%)
Disease in remission at time of conception	29 (19.2%)
Mothers with previous children with AV blocks	3 (2.1%)

BMI: body mass index; AV: atrioventricular

Table 2: Demographic, clinical and immunological characteristics of babies.

Neonatal characteristics	
Birth	
Gestational age, *mean ± SD (weeks^{+days})*	$37^{+6} \pm 1^{+6}$
Preterm birth, *n (%)*	28 (19.7%)
Male gender, *n (%)*	80 (56.3%)
Apgar 1', *median ± SD*	9
Apgar 10', *median ± SD*	10
Admission in the NICU, *n (%)*	25 (17.6%)
Foetal anthropometry	
Length, *mean ± SD (cm)*	47.5 ± 3.5
Weight, *mean ± SD (g)*	2831.0 ± 533.4
Head circumference, *mean ± SD (cm)*	33.5 ± 1.9
Neonatal manifestations, *n (%)*	
NL	7 (4.9%)
Cardiac manifestations	5 (71.4%)
Type I AV block	1 (20.0%)
Type II AV block	1 (20.0%)
Complete AV block	4 (80.0%)
Need for pacemaker	3 (60.0%)
Cutaneous manifestations	2 (28.6%)
Persistence after 6 months	0 (0.0%)
Persistence of atrophic and/ or scarring injuries	1 (50.0%)
Haematological manifestations	2 (28.6%)
Hepatic manifestations	1 (0.0%)
Pulmonary complications	1 (0.7%)
Immunological manifestations, *n (%)*	
ANA positive	2 (1.4%)
Anti-dsDNA positive	1 (0.7%)
Anti-SSA/Ro positive	5 (3.5%)
Anti-SSB/La positive	3 (2.1%)
Positive clinical features of neonatal lupus with lack of immunological information	1 (0.7%)
IgM/IgG anti-ß2GP positive	1 (0.7%)

FGR: intrauterine growth restriction; AV: atrioventricular; NICU: neonatal intensive care unit; NL: neonatal lupus

Table 3: Pregnancy outcome of patients.

	FGR n=19	aFGR n=125	p
Gestation, *n (%)*			
Gestational diabetes	3 (15.8%)	3 (2.4%)	0.030*
Preconception appointment	0 (0.0%)	34 (27.2%)	0.004*
Disease in remission at time of conception	4 (21.1%)	25 (20.0%)	0.561
Systemic lupus erythematosus	6 (31.6%)	47 (37.6%)	0.407
Sjögren's syndrome	3 (15.8%)	13 (10.4%)	0.355
Anti-phospholipid syndrome	8 (42.1%)	29 (23.2%)	0.074
Birth			
Preterm birth, *n (%)*	7 (36.8%)	21 (16.8%)	0.046*
Admission in the NICU, *n (%)*	10 (52.6%)	15 (12.0%)	<0.001*
Apgar 1´, *median*	8.0	9.0	<0.001*
Apgar 10´, *median*	9.0	10.0	<0.001*
Foetal anthropometry, *median*			
Length at birth *(cm)*	45.0	48.0	<0.001*
Weight at birth *(g)*	2195.0	2930.0	<0.001*
Head circumference *(cm)*	32.0	33.5	0.001*
	Preterm birth n=28	aPreterm birth n=114	p
Gestation, *n (%)*			
Babies born of twin pregnancies	6 (21.4%)	2 (1.8%)	0.001*
FGR	7 (25.0%)	10 (8.8%)	0.026*
Glucocorticoid administration	22 (78.6%)	55 (48.2%)	0.003*
Preconception appointment	2 (7.1%)	32 (28.1%)	0.013*
Disease in remission at time of conception	2 (7.1%)	27 (23.7%)	0.038*
Systemic lupus erythematosus	10 (35.7%)	43 (37.7%)	0.513
Sjögren's syndrome	1 (3.6%)	14 (12.3%)	0.158
Anti-phospholipid syndrome	9 (32.1%)	27 (23.7%)	0.244
Birth			
Apgar 1´, *median*	8.0	9.0	0.055
Apgar 10´, *median*	9.0	10.0	<0.001*
Admission in the NICU, *n (%)*	16 (57.1%)	9 (7.9%)	<0.001*
Foetal anthropometry, *median*			
Length at birth *(cm)*	45.0	49.0	<0.001*
Weight at birth *(g)*	2280.0	2962.5	<0.001*
Head circumference *(cm)*	32.5	33.0	0.007*

FGR: intrauterine growth restriction; aFGR: not born with FGR; NICU: neonatal intensive care unit; aPreterm birth: not born preterm. *: statistically significant result

Table 4: Neonatal manifestations of patients

	NL n=7	aNL n=137	p
Gestation, *n (%)*			
FGR	3 (42.9%)	16 (11.7%)	0.049*
Systemic lupus erythematosus	4 (57.1%)	49 (35.8%)	0.226
Sjögren's syndrome	4 (57.1%)	12 (8.8%)	0.003*
Anti-phospholipid syndrome	0 (0.0%)	37 (27.0%)	0.119
Immunological manifestations during pregnancy, *n (%)*			
Anti-SSa/Ro positive	7 (100.0%)	27 (19.7%)	<0.001*
Anti-SSb/La positive	5 (71.4%)	13 (9.5%)	<0.001*
Birth			
Admission in the NICU, *n (%)*	5 (71.4%)	20 (14.6%)	0.002*
Apgar 10´, *median*	9.0	10.0	0.022*
Foetal anthropometry, *median*			
Length at birth *(cm)*	45.5	48.0	0.004*
Weight at birth *(g)*	2665.0	2890.0	0.062
Head circumference at birth *(cm)*	33.0	33.0	0.569
Neonatal immunological manifestations, *n (%)*			
Anti-SSa/Ro positive	5 (71.4%)	0 (0.0%)	<0.001*
Anti-SSb/La positive	3 (42.9%)	0 (0.0%)	<0.001*
Anti-dsDNA positive	1 (14.3%)	0 (0.0%)	0.046*
Anti-ß2GP positive	1 (14.3%)	0 (0.0%)	0.046*
ANA positive	2 (28.6%)	0 (0.0%)	0.002*

NL: neonatal lupus; aNL: not born with neonatal lupus; Anti-: antibody; NICU: neonatal intensive care unit. *: statistically significant result

Anexos

1. Parecer da comissão de ética

2. Normas de publicação de "Journal of autoimmunity"

323-16

Unidade de Investigação

Tomei conhecimento. Nada a opor.

02 de Janeiro de 2017

A Coordenadora da Unidade de Investigação

(Prof.ª Doutora Ana Azevedo)

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10 JAN 2017

Aprovado. Ao CA.

(Prof.ª Doutora Ana Azevedo)

AUTORIZADO

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Exmo. Senhor
Presidente do Conselho de Administração do
Centro Hospitalar de S. João – EPE

Assunto: Pedido de autorização para realização de estudo/projecto de investigação

Nome do Investigador Principal: José Miguel Barreto Bernardo

Título do projecto de investigação: Neonatal manifestations of immune-mediated rheumatic diseases: a retrospective longitudinal study.

Pretendendo realizar no(s) Serviço(s) de Neonatalogia e Ginecologia/Obstetrícia do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efectivação.

Para o efeito, anexa toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de S. João respeitante a estudos/projectos de investigação, à qual endereçou pedido de apreciação e parecer.

Com os melhores cumprimentos.

Porto, 24 / Outubro / 2016

O INVESTIGADOR/PROMOTOR

José Bernardo

Comissão de Ética para a Saúde do C.H.S.João e da FMUP

Parecer

Título do Projecto: Neonatal manifestations of immune-mediated rheumatic diseases:a retrospective longitudinal study

Nome do Investigador Principal: José Miguel Barreto Bernardo

Promotor do Estudo: NA

Serviço onde decorrerá o Estudo: Serviço de Neonatalogia e Serviço de Ginecologia e Obstetrícia do Centro Hospitalar de S. João

Objectivo e Pertinência do Estudo: Com este projecto de investigação, pretende-se "estudar a prevalência das manifestações das doenças auto-imunes neonatais em recém-nascidos de mulheres com doença auto-imune diagnosticada previamente ou durante a gravidez, com os casos presentes nos últimos 16 anos na consulta de doenças auto-imunes obstétricas do CHSJ, estudando o período de gravidez e as manifestações neo-natais nos recém-nascidos". Trata-se de um estudo retrospectivo e o desenho que lhe é dedicado adequa-se aos objectivos pretendidos. O acesso aos processos clínicos será realizado através dos Elos de ligação.

Benefício/risco: NA

Respeito pela liberdade e autonomia do sujeito de ensaio: NA

Confidencialidade dos dados: A confidencialidade da informação recolhida será suportada na codificação e inerente anonimização dos dados.

Elo de ligação: Doutora Hercília Guimarães (Serviço de Neonatalogia) e Doutor Nuno Montenegro (Obstetrícia e Ginecologia)

Indemnização por danos: NA

Continuação do tratamento: NA

Propriedade dos dados: Os dados não serão propriedade exclusiva do Promotor/Investigador, e estão-lhe referidos critérios de divulgação dos resultados a alcançar.

Curriculum do investigador: Adequado ao perfil da investigação.

Data previsível da conclusão do estudo: Fevereiro de 2017

Conclusão: Considerados os objectivos do estudo e a metodologia que lhe está prevista, proponho um parecer favorável à realização deste projecto de investigação na sua actual definição metodológica.

Porto e H.S.João, 2016-11-18

O relator

Doutor Filipe Almeida

7. SEGURO

a. *Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?*

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)
NÃO ☐
NÃO APLICÁVEL ☑

8. TERMO DE RESPONSABILIDADE

Eu, José Miguel Barreto Bernardo,
abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 24 / Outubro / 2016

José Bernardo

O Investigador Principal

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO

emitido na reunião plenária da CES de 18 / Novembro / 2016

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.

JOURNAL OF AUTOIMMUNITY

AUTHOR INFORMATION PACK

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The *Journal of Autoimmunity* publishes papers related to the diverse aspects of **autoimmunity**: the mechanism of self-recognition, regulation of **autoimmune responses**, experimental **autoimmune diseases**, diagnostic **autoantibody** tests, and the **epidemiology**, **pathophysiology**, and treatment of autoimmune diseases. Special, but not exclusive, attention will be given to papers dealing with genetic, molecular biology, and cellular aspects of the discipline.

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Apêndice

1. Agradecimentos

Agradecimentos

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E por fim, agradeço à Doutora Mariana Guimarães, na nossa forma de comunicação:

Gott spricht zu jedem nur, eh er ihn macht,
dann geht er schweigend mit ihm aus der Nacht.
Aber die Worte, eh jeder beginnt,
diese wolkigen Worte, sind:

Von deinen Sinnen hinausgesandt,
geh bis an deiner Sehnsucht Rand;
gieb mir Gewand.
Hinter den Dingen wachse als Brand,
daß ihre Schatten, ausgespannt,
immer mich ganz bedecken.

Laß dir Alles geschehn: Schönheit und Schrecken.
Man muß nur gehn: Kein Gefühl ist das fernste.
Laß dich von mir nicht trennen.
Nah ist das Land,
das sie das Leben nennen.

Du wirst es erkennen
an seinem Ernste.

Gieb mir die Hand.

Rainer Maria Rilke, Das Stundenbuch (1899)